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## Traumatic brain injury 1

# Severe traumatic brain injury: targeted management in the intensive care unit

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This is the first in a *Series* of four papers about traumatic brain injury

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Severe traumatic brain injury (TBI) is currently managed in the intensive care unit with a combined medical–surgical approach. Treatment aims to prevent additional brain damage and to optimise conditions for brain recovery. TBI is typically considered and treated as one pathological entity, although in fact it is a syndrome comprising a range of lesions that can require different therapies and physiological goals. Owing to advances in monitoring and imaging, there is now the potential to identify specific mechanisms of brain damage and to better target treatment to individuals or subsets of patients. Targeted treatment is especially relevant for elderly people—who now represent an increasing proportion of patients with TBI—as preinjury comorbidities and their therapies demand tailored management strategies. Progress in monitoring and in understanding pathophysiological mechanisms of TBI could change current management in the intensive care unit, enabling targeted interventions that could ultimately improve outcomes.

## Introduction

Traumatic brain injury (TBI) is a major cause of death and disability worldwide, with more than 13 million people estimated to live with disabilities related to TBI in Europe and the USA.<sup>1</sup> About 10–15% of patients with TBI have serious injuries that require specialist care.<sup>2</sup> Patients with severe grades of TBI are commonly managed in the intensive care unit (ICU)<sup>3</sup> with a combined medical–surgical approach that has changed little over the past 20 years. A reassessment of this area of clinical practice is warranted on several grounds. First, recent expert reappraisals of such care have indicated that the evidence supporting most interventions is weak or non-existent,<sup>4</sup> with few randomised controlled trials (RCTs) to guide treatment decisions. In view of this dearth of evidence-based medicine to underpin clinical care, clinicians have had to rely on best-practice statements from expert bodies, based on decades of accumulated and refined clinical experience.<sup>5</sup> Moreover, treatment targets incorporated into guidelines are usually derived from population studies and applied to all patients with TBI in the ICU. This approach reduces management variability but ignores differences in underlying pathological features. TBI is, in fact, a syndrome that includes a range of brain lesions with separate—sometimes diverging—pathophysiological pathways and therapeutic needs. As a result, undifferentiated interventions aimed at the overall population with TBI, rather than targeted to specific disease mechanisms and groups of patients, are likely to fail, as exemplified by repeated failures of clinical trials of neuroprotective agents.<sup>6</sup>

Furthermore, many patients with TBI who are now treated in the ICU differ greatly from those individuals from whom much of our accumulated clinical experience, research, and guidelines have been derived—ie, young (typically male) patients who sustained a TBI from

high-velocity traffic injuries or assault. In high-income countries, TBI affects increasing proportions of people older than 65 years (who we arbitrarily indicate as elderly)—eg, in the USA, the rate of TBI-related hospital admissions for elderly people has risen by more than 50% from 2001 to 2010,<sup>7</sup> whereas this rate has remained stable or declined for individuals aged 15–44 years. This epidemiological change reflects increased life expectancy<sup>8</sup> coupled with risk factors typical of elderly people, such as age-related comorbidities and their pharmacological treatment. These older patients typically present after having sustained falls from a fairly low height, and the clinical course of these TBIs is complicated by multiple comorbidities and their treatment.

In this Review, we briefly describe the heterogeneity of pathological and pathophysiological features of TBI seen in the ICU, discuss how we might organise rational clinical care in view of the scarcity of conventional evidence from RCTs, and postulate how we could individualise care to aim for precision medicine approaches, considering pathophysiological diversity with use of advances in monitoring techniques. We focus on severe TBI in adults and, importantly, in addressing each of these issues, we examine how the rising age of patients with TBI in the ICU might require new evidence to strengthen clinical management.

## Pathological and pathophysiological features

### Primary and secondary injury

TBI is divided classically into two distinct phases: primary injury followed by delayed secondary injury. Primary injury arises from external physical forces applied to the head producing skull fractures, haematomas, and deformation and destruction of brain tissue, including contusions and axonal injury. Secondary injury develops over time with activation of multiple molecular and cellular pathways.<sup>9,10</sup> Axonal stretching

during injury can cause dysregulation of transmembrane ion fluxes and impaired axonal transport, and damaged axons could be vulnerable to secondary axotomy and demyelination. Changes in ionic permeability and release of excitatory neurotransmitters, particularly glutamate, propagate damage through energy failure and overload of free radicals. Altered cellular permeability also increases calcium influx, which causes mitochondrial dysfunction, triggering further energy defects and necrotic and apoptotic processes.<sup>10</sup>

These molecular and cellular changes might lead to development of cytotoxic or vasogenic brain oedema and disturbed autoregulation, whereby the volume of intracranial contents grows because of vascular dilation or water accumulation, or both.<sup>11</sup> Once this volume increase exceeds the compensatory capacities of the intracranial space, intracranial pressure (ICP) rises. Seizures early after trauma can exacerbate the imbalance between energy expenditure and supply.<sup>12</sup> Another electrical disturbance—spreading depolarisation—can occur in patients with TBI, and might be responsive to glutamate antagonists. Spreading depolarisation leads to anaerobic metabolism and energy substrate depletion, and it also seems to be associated with a worse outcome.<sup>13</sup>

Trauma affects the blood–brain barrier directly, with increased permeability favouring vasogenic oedema formation and activation of a proinflammatory state.<sup>14</sup> Inflammation, also promoted by resident microglia, could provide neuroprotection or aggravate secondary injury.<sup>14</sup> Patients with TBI often have extracranial injuries (eg, fractures and chest and abdominal trauma) and massive bleeding. These can cause hypoxia or arterial hypotension and trigger a systemic inflammatory response syndrome that can further aggravate the development of secondary injury.<sup>15</sup> This complex series of events starts minutes after trauma but lasts for weeks or even months, particularly for inflammation.<sup>16</sup>

### Heterogeneity of TBI

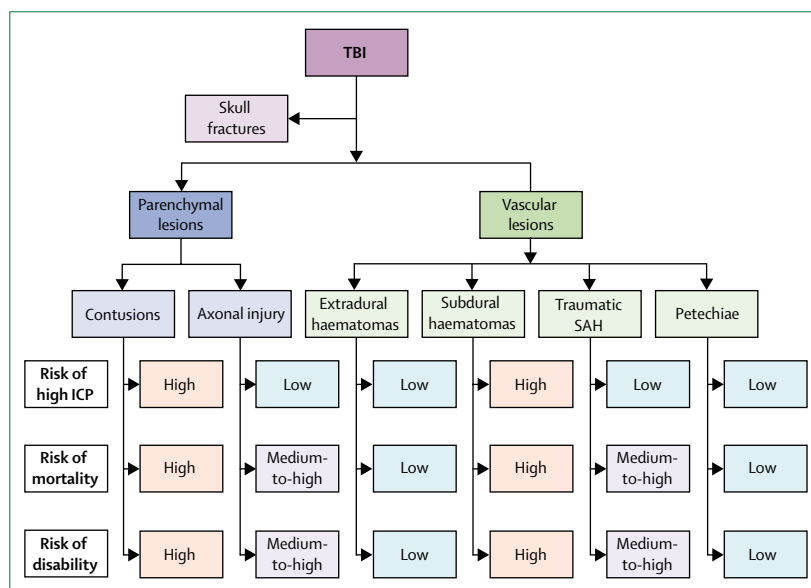
TBI is typically classified according to clinical severity, with severe injury usually categorised on the basis of a total Glasgow Coma Scale (GCS) score of 8 or less.<sup>17</sup> TBI produces various lesions that range from mild injury to devastating damage. Expanding haematomas—extradural or subdural—might need emergency surgical removal in the first hours after injury; intraparenchymal contusions can increase over hours or days and need surgery as well. More subtle lesions such as traumatic axonal injury (the term commonly used, diffuse axonal injury, strictly only applies when involving three or more locations<sup>18</sup>) might not be evident from initial CT scans but, owing to neuronal network disruption, might have a serious effect on the quality of life of survivors, and can be seen on MRI.<sup>19</sup> These different lesion types typically arise in combination: for instance, cerebral contusions can develop underneath a subdural haematoma, and might

also be associated with axonal injury. Figure 1 shows how the risk of high ICP, mortality, and disability can vary by lesion type.<sup>20–23</sup>

Several biomarkers of neuronal injury (eg, neuron-specific enolase, ubiquitin C-terminal hydrolase L1, spectrin breakdown products), axonal injury (eg, tau protein, neurofilaments), and glial injury (eg, glial fibrillary acidic protein, S100 $\beta$ ) in serum and CSF are being investigated in patients with TBI.<sup>24,25</sup> These markers could—either individually or in combination—be used to characterise injury severity and type, and they might have prognostic importance.<sup>24,25</sup> Although preliminary evidence of cost-effectiveness is emerging for some biomarkers in mild TBI, their role in more severe injury remains uncertain. We need large-scale studies of the most promising biomarkers (or panels of biomarkers) to determine whether they can be used to refine initial characterisation of brain damage in critically ill patients with TBI.

### Specific features of TBI in elderly people

TBI in older patients typically results from low-energy impacts such as ground-level falls,<sup>26</sup> with a higher



**Figure 1: Heterogeneity of traumatic brain injury**

Road accidents, intentional injuries, and falls can cause different types of head lesion; together with skull fractures, various parenchymal and vascular injuries often coexist. In this schematic diagram, lesions are presented separately for the purpose of classification, and estimates of risk of high ICP, mortality, and disability are shown. Some lesions, such as subdural haematomas, entail a substantial risk of elevated ICP, whereas others, such as axonal injury, are associated rarely with ICP disturbances<sup>20</sup> but might have a very severe effect on outcome. Axonal damage in multiple brain regions causes impairments in cognitive, motor, and sensory functions by disrupting neuronal connectivity. Pathological masses, such as contusions or intracranial haematomas, can vary in size and in their tendency to expand. When large pathological volumes accumulate, further compressing the brain, the probability of an unfavourable outcome, with high mortality and severe disability, is raised. Other vascular injuries, such as major vessel dissection or traumatic aneurysms, perhaps underdiagnosed with routine imaging, can be detected with appropriate investigations.<sup>21</sup> Mortality and disability are associated with several factors, such as age, comorbidities, and location and extent of the traumatic injury. Similarly, ICP rises might depend on multiple disturbances, such as hyponatraemia, and not just on the initial anatomical damage. Information on outcomes is from the IMPACT study.<sup>22,23</sup> ICP=intracranial pressure. SAH=subarachnoid haemorrhage. TBI=traumatic brain injury.

proportion of subdural haematomas and fewer contusions or epidural haematomas in this group than in younger patients.<sup>27,28</sup> Cerebral atrophy and increased CSF space could buffer new pathological intracranial masses, which could be linked to a lower incidence of raised ICP.<sup>29,30</sup> The GCS might underestimate the severity of brain injury in elderly patients,<sup>31</sup> making a case for higher score thresholds to trigger triage of older patients to specialist centres.<sup>32</sup> Furthermore, age-related comorbidities (eg, diabetes, chronic cardio-respiratory disease, and renal dysfunction) reduce physiological reserve and increase the incidence and severity of brain damage due to second insults such as hypoxia and hypotension. Many of the treatments used for these chronic diseases (in particular, anticoagulant and antiplatelet drugs) might increase risk of haemorrhage or could worsen the evolution of intracerebral traumatic lesions (with the greatest risk from vitamin K antagonists).<sup>33</sup> Finally, the diminished brain reserve in these older patients<sup>34</sup> limits the potential for plasticity and neural repair and, hence, hampers the success of rehabilitation. The main differences between younger and older patients with TBI are summarised in the panel.<sup>34–44</sup>

## Fundamentals of ICU monitoring and management

Patients with severe TBI are currently treated in the ICU with a specialised neurointensive approach combined with strategies used in general intensive care such as early enteral feeding, infection control and treatment, normalisation of respiratory exchanges with skilled nursing, physiotherapy, and artificial ventilation, and fluid optimisation for arterial pressure and splanchnic organ perfusion. This approach aims to prevent second insults and maintain cerebral homeostasis. Some current strategies entail targeted approaches—eg, surgical haematoma removal—whereas many medical therapies (for instance, treatments for controlling high ICP) are prescribed for all cases.

### Prevention of second insults

Prevention of second insults involves addressing both systemic threats (eg, hypoxia, hypercapnia, arterial hypotension, hyponatraemia, and pyrexia) and intracranial threats (eg, expanding haematomas or contusions and ICP rises). In this section, we focus on intracranial threats, which can be detected through clinical examination and ICP monitoring.

#### Panel: Main differences between young adults and elderly people with traumatic brain injury

##### Preinjury factors

- Comorbidities are common in elderly people but rare in young adults with traumatic brain injury (TBI). Diabetes, chronic heart and renal failure, and chronic obstructive pulmonary disease might all increase the risk of systemic complications and second insults such as hypoxia and hypotension.
- Anticoagulant and antiplatelet drugs are used increasingly in the general population,<sup>35</sup> and particularly in elderly people; these drugs increase the risk of cerebral haemorrhagic lesions and might worsen the expansion of initial bleeding, even after modest TBIs.<sup>36,37</sup>
- Polypharmacy—including sedatives or hypnotics, antidepressants, benzodiazepines, and antihypertensive drugs—is common in elderly patients but not in young adults; these drugs might increase instability and predispose patients to a fall.<sup>38</sup>
- Elderly patients have less brain reserve than younger patients,<sup>34</sup> a vulnerability that amplifies the result of brain damage and hampers rehabilitation.
- Pre-existing neurodegenerative diseases that reduce cognitive reserve and impair motor function can increase the risk of TBI in affected elderly people.

##### Cause of injury

- Ground-level falls and low-energy impacts are typical of TBIs in the elderly population,<sup>7,26,28,39</sup> and these injuries are associated with impaired mobility and polypharmacy.<sup>38</sup>
- TBIs in young adults are often secondary to high-energy impacts from road traffic accidents or assaults.<sup>7,39</sup>

##### Type of lesion

- The proportion of subdural haematomas diagnosed in older patients is higher than in young adults; these haematomas are typically associated with lower severity and less underlying brain injury in older patients.
- The proportion of contusions, epidural haematomas, and axonal injury lesions diagnosed in young adults is higher than in elderly patients.<sup>27,28</sup>

##### Clinical course

- The initial Glasgow Coma Scale score might be inappropriately high and not reflect the severity of structural injury in elderly patients.<sup>31</sup>
- Older patients often have delays with CT imaging, are less likely to be transferred to specialist neurosurgical facilities, and are more usually cared for by junior medical staff.<sup>44</sup>
- Elderly patients have a lower incidence of raised intracranial pressure than do younger patients, which could be attributable to cerebral atrophy and an increased CSF space that buffers new pathological intracranial masses.<sup>29,30</sup>
- Post-traumatic seizures are more common in older patients than in young adults.<sup>40</sup>
- Compared with young adults, elderly people have poorer functional outcomes and higher mortality, more medical complications during their stay in the intensive care unit (requiring in-hospital procedures), and longer hospital stays and continued medical care.<sup>27,41–43</sup>

### Neurological clinical examination

Clinical examination remains a fundamental monitoring procedure, even in patients who are comatose or sedated, to identify neurological deterioration and potential indications for surgical interventions. The basic examination relies on a GCS assessment coupled with investigation of pupil diameter and reactivity to light. There are some obstacles to a complete GCS assessment: tracheal intubation precludes a verbal response and facial injuries can impede eye opening, so motor response remains the main assessable component of the GCS score. Neurological evaluation in patients who are deeply sedated can require a sedation hold (wake-up test), which might cause arterial hypertension and—in patients with reduced intracranial compliance—transient rises in ICP.<sup>45</sup> Whether these ICP spikes are detrimental for brain homeostasis is uncertain.<sup>46,47</sup> Nevertheless, a wake-up test could help to identify important clinical changes—eg, signs of progressive brainstem impairment, rapid improvement after successful surgical removal of intracranial masses, or intoxication with alcohol or other substances. This test could affect a patient's management profoundly, with more aggressive intervention in patients who show deterioration or shorter intubation and ventilation times in those recovering favourably.

Assessments of pupillary diameter and reactivity are vital.<sup>48</sup> A dilated unreactive pupil usually discloses compression of the third cranial nerve due to midline shift and uncal herniation.<sup>49</sup> Pupillary reaction to light is assessed typically using a flashlight, although this method has poor inter-rater accuracy in clinical practice.<sup>50</sup> Automated pupillometry is a portable technique that measures pupil size and light reactivity automatically and with a high degree of precision.<sup>51</sup> This method might give more accurate measurements of reactivity, particularly when the pupil is small (eg, with opioid analgesia).<sup>51</sup>

Up to 40% of patients with TBI show substantial worsening during the first 48 h in the ICU.<sup>52</sup> Neurological worsening is currently defined as a decrease of 2 points on the GCS motor component, pupil asymmetry or loss of pupillary reactivity, or deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention.<sup>18</sup> Neurological worsening in TBI is associated significantly with high ICP and poor outcome.<sup>53,54</sup> This deterioration is typically due to a new or expanding intracranial lesion that might need surgical evacuation. Understanding of neurological worsening is becoming increasingly important because prompt access to early CT means that patients are usually scanned within minutes after the TBI, before lesions have had a chance to appear or evolve. Parenchymal lesions can expand over hours or days: in a series of 352 cases with contusions followed up with three CT scans, the volume of haemorrhage increased in 42% of patients.<sup>55</sup> A routine second CT scan is, therefore, recommended for all patients with TBI who are comatose, which might

disclose surgical lesions in up to a third of cases.<sup>56</sup> Additionally, if any substantial clinical worsening occurs or ICP rises, a new CT scan must be done.<sup>56</sup>

### ICP monitoring

ICP measurement is done through ventricular or intraparenchymal probes connected to a monitor.<sup>11</sup> This monitoring has been the cornerstone of TBI care since the 1980s. However, in a multicentre trial from South America (BEST:TRIP),<sup>57</sup> ICU management based on repeated clinical examination and CT scans was not inferior to management including continuous measurement of ICP. It would be entirely inappropriate to discard the role of ICP monitoring on the basis of the findings of this study,<sup>58</sup> but it does highlight the difficulties with postulating a direct link between monitoring and improvement of outcome, which can be too simplistic when considered in isolation.

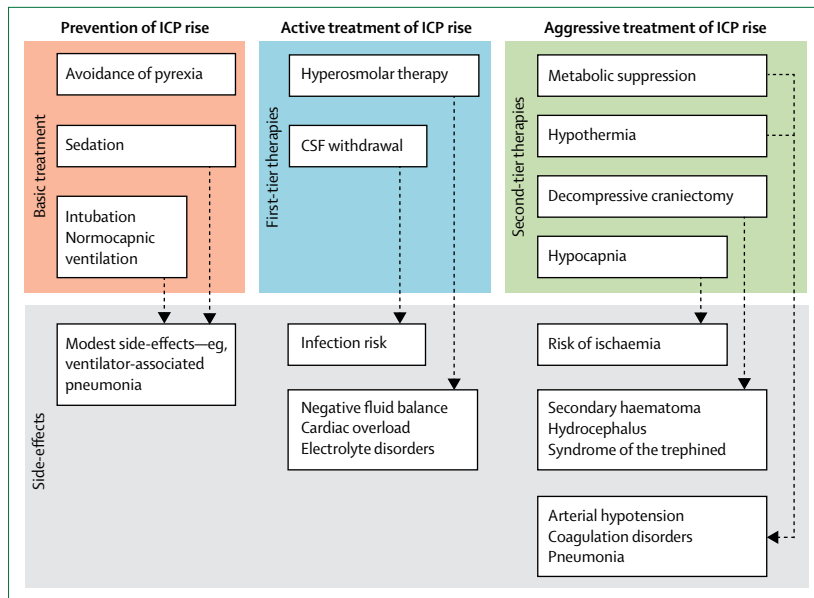
In the 4th edition of the Brain Trauma Foundation guidelines, ICP monitoring is indicated in patients with severe TBI, because evidence suggests that ICP-guided treatment can reduce early mortality.<sup>4</sup> A variable proportion of patients with severe TBI develop raised ICP, generally depending on the definition. The historical and most widely accepted ICP threshold for therapy is 20 mm Hg, although the latest guidelines suggest 22 mm Hg.<sup>4</sup> This approach, which is based on population targets, provides little potential for optimising therapy according to the needs of individual patients. Indeed, available published work suggests that there could be subtle differences in critical ICP thresholds between young and old and male and female patients, even at an aggregated population level, with older patients (age  $\geq 55$  years) and females having lower ICP thresholds (18 mm Hg vs 22 mm Hg) for prediction of poor outcome.<sup>59</sup>

Protocols for ICP therapy vary in detail but generally include prevention of ICP rises using mechanical ventilation, sedation, and avoidance of pyrexia (figure 2), as well as active interventions.<sup>11</sup> For increases in ICP, first-tier strategies include oedema management with hyperosmotic infusions and drainage of CSF (when a ventricular drain is available). More aggressive therapies are required for refractory ICP, including hypothermia, metabolic suppression with deep sedation, decompressive craniectomy, and hypocapnia, but these can have harmful side-effects (figure 2).<sup>60,61</sup> ICP monitoring is fairly safe; complications such as haemorrhage and infection arise in 1–7% of cases,<sup>62</sup> driving a search for non-invasive alternatives. Several methods are under investigation for non-invasive ICP measurement but are not yet ready for clinical use.<sup>11</sup>

### Maintenance of cerebral homeostasis

Maintenance of cerebral homeostasis and, in particular, optimisation of cerebral oxygen supply and demand are traditionally attempted using indirect variables such as cerebral perfusion pressure (CPP), which is the difference





**Figure 2: Current prevention and treatment of intracranial hypertension after traumatic brain injury**

Surgical removal of intracranial masses is the most effective treatment for intracranial hypertension in the early phases after TBI. After surgery, strategies for ICP control are graded from prevention to progressively more intensive treatments. Prevention of high ICP is based on standard procedures in the intensive care unit, with fairly modest side-effects, such as ventilator-associated pneumonia for prolonged artificial ventilation. First-tier active interventions include CSF withdrawal (which requires a ventricular drain, with the risk of ventriculitis) and hyperosmolar drugs, such as mannitol or hypertonic saline (with the risks of cardiac overload during infusion and dehydration and hyperosmolar states due to induced diuresis).<sup>31</sup> Second-tier interventions include more aggressive treatments with associated risk of severe complications. Preventive measures are usually used for all patients with severe TBI, whereas active treatment is triggered by ICP rises. This approach is based mainly on clinical experience rather than on strong published evidence.<sup>4</sup> Because of side-effects, interventions effective at reducing ICP might not translate directly into improved outcomes.<sup>60,61</sup> ICP=intracranial pressure. TBI=traumatic brain injury.

between mean arterial blood pressure and ICP. Ideally, normal arterial pressure coupled with a physiological ICP value should be maintained. In cases of arterial hypotension, vasopressors and volume expansion are used to restore an adequate arterial pressure whereas ICP becomes a target when it exceeds a threshold. CPP of around 60 mm Hg is generally targeted, although the latest guidelines suggest some discrimination between individuals with and without preserved autoregulation.<sup>4</sup> However, as with ICP, these guidelines do not account for differences in CPP thresholds between groups of patients.<sup>59</sup>

#### Modulatory effects of age

A clear association has been noted between older age and worse outcome,<sup>42,43</sup> which could be accounted for, at least in part, by the effects of age-related comorbidities,<sup>63</sup> use of pharmacotherapies to treat comorbidities (particularly antithrombotic drugs),<sup>37</sup> and reduced brain reserve in elderly patients.<sup>34</sup> Treatment and monitoring of comorbidities might, therefore, be as important as management of TBI in determining outcome.<sup>63</sup> Treatment of drug-induced coagulopathy with reversal of anticoagulant or antiplatelet therapy is essential if an intracranial haemorrhage is present.<sup>64,65</sup> Post-traumatic seizures are common in older patients with TBI;<sup>40</sup>

however, the optimum therapy and length of seizure prophylaxis in this population is still not clear.

An unfavourable outcome in older patients could be, at least in part, a self-fulfilling prophecy. Data gathered for 4387 patients with TBI in the UK indicate suboptimum care for older patients, including delayed CT scans, assessment more commonly by junior medical staff, and a reduced likelihood of being transferred to neurotrauma centres (panel).<sup>44</sup> However, when older patients are treated aggressively and promptly after admission to the ICU, favourable outcomes are seen in 39% of patients aged 60–69 years,<sup>27</sup> suggesting that this nihilistic attitude is not justified.

The lower ICP threshold associated with poor outcome in older patients compared with younger people (18 mm Hg vs 22 mm Hg)<sup>59</sup> might reflect the greater vulnerability of the aged brain, or a given rise in ICP might denote a worse brain injury in older patients, since age-related atrophy and increased CSF space allows lesion expansion and brain oedema before ICP rises. Notwithstanding the cause, these data provide the rationale for investigating whether a reduced threshold for ICP control might be beneficial in older patients. However, because increased ICP is less frequent in elderly populations, and tissue penetration by intracranial probes is riskier in patients who have received anticoagulant and antiplatelet drugs, there is a case for revised (reduced) indications for ICP monitoring in these patients.

Elderly patients might also have compromised autoregulation because of arterial hypertension, with the autoregulatory curve shifted towards higher arterial pressure. Indeed, available data suggest that CPP thresholds for survival are higher in patients older than 55 years than in younger patients,<sup>59</sup> and a higher CPP might be desirable, particularly in patients with a history of arterial hypertension.<sup>4,59</sup>

It is worth noting that the current conceptual basis of ICU management of TBI is based on a body of experience accumulated over the past four decades, which derives overwhelmingly from younger patients with high-velocity injuries. It would be wrong, or at least unsafe, to assume that this experience can be directly applied to the older patients we see with different injury mechanisms (panel), and there is a pressing need to develop optimum management strategies targeted to these patients.

#### Targeted ICU management based on physiological monitoring

Clinical pathophysiology of TBI is dependent on the patient, the treatment given, and the type of injury and, therefore, is highly heterogeneous. A one-size-fits-all management strategy is unlikely to be optimum. More precise understanding of intracranial disturbances might indicate specific targets and, hopefully, targeted therapies. A panoply of monitoring techniques (table 1) and imaging modalities (table 2) can be used to obtain this information, including measurement of brain tissue partial tension

	Variable monitored	Variable derived	Focal or global measure	Time resolution	Risk of brain damage	Running costs (€)*	Other limitations
Intracranial pressure monitoring with intraparenchymal monitor or ventricular catheter	Intracranial pressure	Intracranial volumes, cerebral perfusion pressure, pressure-reactivity index, intracranial compliance	Global	Continuous	Yes	<50	None
Brain tissue oxygen measurement with parenchymal probe	Brain tissue partial tension of oxygen	Oxygen diffusion and balance between oxygen supply and demand	Focal	Continuous	Yes	50–500	None
Cerebral microdialysis	Brain metabolites and biomarkers	Aerobic or anaerobic metabolism, brain injury severity and inflammation	Focal	Intermittent	Yes	>500	None
Temperature monitoring via intraparenchymal probe	Brain temperature	Gradient between core and brain temperature	Focal	Continuous	Yes	50–500	None
Intraparenchymal thermal diffusion flowmetry	Cerebral blood flow	Hypoperfusion or hyperperfusion	Focal	Continuous	Yes	>500	Non-standard technique
Electrocorticography	Cortical and depth electrical activity	Seizure activity, spreading depolarisation	Focal	Continuous	Yes	>500	Requires specific surgical placement
Jugular bulb oximetry	Oxygen saturation of venous jugular haemoglobin	Cerebral artero-jugular difference in oxygen content	Global	Intermittent (continuous with fiberoptic catheters)	No	<50 (50–500 for fiberoptic catheters)	None
EEG	Cortical electrical activity	Seizure activity, abnormal patterns	Global	Continuous	No	<50	Training needed
Transcranial doppler	Cerebral blood velocity	Critical closing pressure, cerebral arterial impedance	Global	Intermittent	No	<50	Operator-dependent
Optic-nerve sheath ultrasonography	Optic nerve-sheath diameter	Intracranial pressure	Global	Intermittent	No	<50	Operator-dependent
Near-infrared spectroscopy	Cerebrovascular oxygen saturation and relative blood volume	Cerebral blood flow, cerebral autoregulation	Focal	Continuous	No	50–500	Extracerebral contamination of signal

The most commonly used bedside technologies are listed.<sup>66</sup> \*Based on information provided by device vendors in most European countries; monitors, personnel, and maintenance are not considered.

**Table 1: Current bedside neuromonitoring modalities for traumatic brain injury**

of oxygen (PbtO<sub>2</sub>), microdialysis, and autoregulation assessment.<sup>66</sup> In isolation, these techniques generally provide indirect measures of TBI pathological processes. For example, raised ICP is not a diagnosis by itself: it results from many (usually coexisting) mechanisms, including oedema (either cytotoxic or vasogenic), increased cerebral blood volume (which itself might result from many disparate mechanisms, including excessive metabolic demand, hypercapnia, or disordered autoregulation), or impaired CSF reabsorption. Methods to better characterise pathophysiological derangements have been available in the past two decades; however, they have been used rarely, even in the most specialised neurological ICUs. Findings of a survey of 31 specialised ICUs in the UK showed that ICP monitoring was used frequently in all but one institution, PbtO<sub>2</sub> measurement in eight (26%), and microdialysis in only four (13%) centres.<sup>67</sup>

### Measurement of PbtO<sub>2</sub>

ICP and CPP provide information on the driving pressure for blood flow through the cerebral circulation. However, downstream metabolic events can also be monitored using several probes, typically through a common insertion device. One such example is measurement of PbtO<sub>2</sub>,<sup>68–70</sup> which provides a continuous (albeit localised) spatial average of extracellular oxygen tension as an indicator of the adequacy of oxygen delivery. PbtO<sub>2</sub> depends on the balance between oxygen delivery

and consumption, and the cerebral metabolic rate of oxygen. It is affected further by the ability of oxygen to diffuse.<sup>71,72</sup> For example, in pericontusional tissue, diffusion of oxygen might be affected not only by tissue and endothelial oedema but also by microvascular collapse, which increases the mean intercapillary distance for diffusion, reducing average oxygen tension.<sup>72</sup>

Determining appropriate target values for PbtO<sub>2</sub> is clearly methodologically difficult: oxygen tensions of around 23 mm Hg are recorded during or after functional neurosurgery.<sup>73</sup> Values between 15 mm Hg and 20 mm Hg are typically regarded as thresholds for inadequate oxygen supply<sup>74–76</sup> and are associated with worse outcome after TBI.<sup>77</sup> Therapeutic approaches have been described that aim to return PbtO<sub>2</sub> to normal levels by increasing either arterial pressure or arterial oxygen tension, or both.<sup>77,78</sup> Those strategies seem to be associated with better outcomes than strategies focused only on ICP and CPP. However, without large controlled trials, evidence is inconclusive.<sup>79</sup>

### Microdialysis

Measurement of glucose, lactate, and pyruvate in the extracellular space of the brain using cerebral microdialysis provides information on energy metabolism. A high lactate:pyruvate ratio after TBI is a marker of anaerobic glucose utilisation, resulting from low PbtO<sub>2</sub> due to ischaemia or diffusion hypoxia or, under normoxic conditions, mitochondrial dysfunction.<sup>80–82</sup> A high

	Variable monitored	Information derived	Spatial resolution	Radiation absorption	Acquisition time (min)	Other limitations
CT	Structural integrity	Space-occupying lesions, CSF space modifications, skull fractures, brain swelling	Medium	Low	<5	Limited resolution for posterior fossa pathology
CT angiography	Cerebral vessel patency and integrity	Thrombosis and dissection in main intracranial vessels	Medium	Medium	<5	Contrast medium injection needed
Perfusion CT	Cerebral perfusion	Hypoperfusion or hyperperfusion	Low	High	<5	Contrast medium injection needed
MRI	Structural, functional, and biochemical integrity, cerebral vessel patency	Space-occupying lesions, CSF space modifications, brain swelling, thrombosis and dissection in main intracranial vessels, hypoperfusion or hyperperfusion, traumatic axonal injury, functional and chemical information	High	None	>20	Magnetic field environment might be contraindicated in some patients,* high cost

\*MRI use is not possible in patients who have indwelling probes containing ferromagnetic material or in patients who are dependent on ventilators, infusion pumps, or monitors used in the intensive care unit for which magnetic resonance safety is unknown. Some magnetic resonance studies can be prolonged and might be contraindicated in unstable patients.

**Table 2: Current imaging modalities for traumatic brain injury**

lactate:pyruvate ratio indicates an energy metabolism crisis and is an independent predictor of mortality.<sup>83</sup> Improvement in the lactate:pyruvate ratio might indicate a beneficial effect of treatment. The effects of various interventions—eg, hyperoxia and hypertonic lactate—on brain energy metabolism have been investigated. Normobaric hyperoxia, which is usually induced by increasing the fraction of inspired oxygen, can typically raise a low PbtO<sub>2</sub>, but inconsistent benefits on microdialysis variables have been reported.<sup>84,85</sup> However, findings of imaging studies suggest improvements in the cerebral metabolic rate of oxygen<sup>86</sup> and reversal of pericontusional cytotoxic oedema with this intervention.<sup>87</sup> Attempts to improve brain glucose metabolism with hypertonic lactate infusions show a clear cerebral glucose-sparing effect, but mainly in patients with a pathological lactate:pyruvate ratio.<sup>88</sup> These preliminary clinical trial results need to be confirmed with larger numbers of participants, but early findings indicate the possibility for targeted interventions.

#### Autoregulation assessment

Methods for online real-time assessment of cerebrovascular autoregulation, a physiological mechanism that serves to maintain adequate cerebral perfusion in the presence of blood pressure changes, have been studied.<sup>66</sup> Under typical conditions, with normal autoregulation, the diameter of cerebral vessels changes to adjust for alterations in arterial pressure (eg, vasoconstriction in response to arterial hypertension) and these changes can affect ICP. In the case of vasoconstriction, ICP should remain unaffected or it could decrease. ICP measurements can, therefore, be used to assess how brain vessels react to variations in arterial pressure. In pathological conditions such as severe TBI, autoregulation can be altered or totally lost. Probably the best known measurement is the pressure-reactivity index

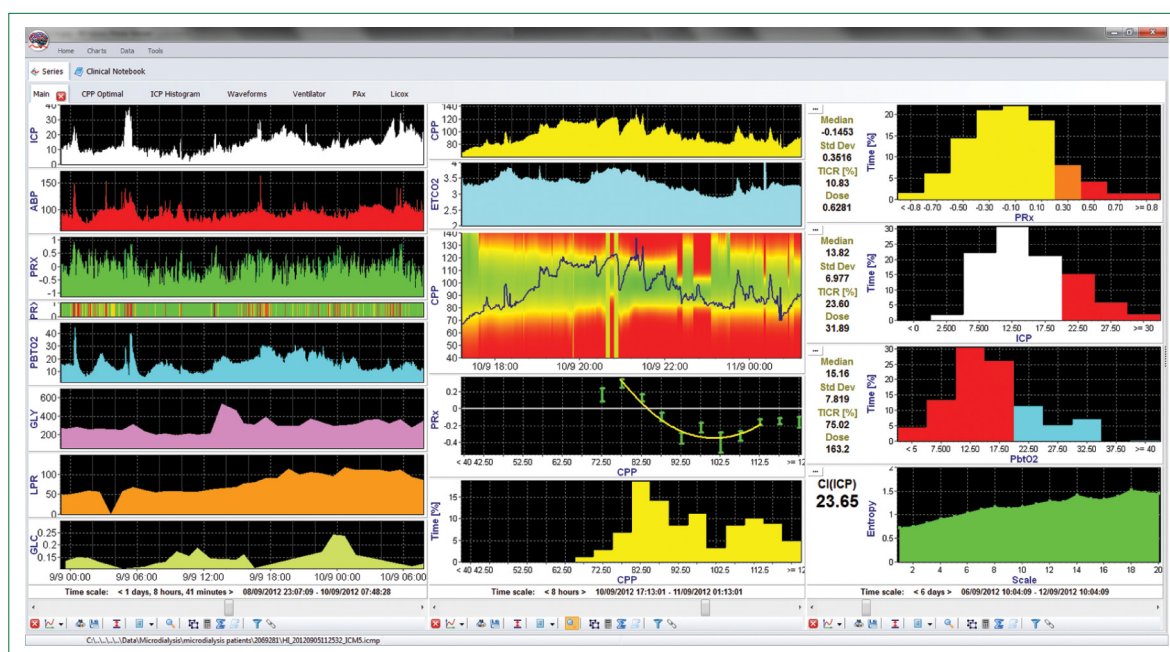
(PRx)—ie, the correlation coefficient between ICP and arterial pressure readings using a moving data window, which is usually a negative number.<sup>89–91</sup> The PRx typically shows a U-shaped relation when plotted against spontaneous changes in CPP over time, with the lowest PRx noted in the optimum autoregulatory range. The CPP for which the PRx is a minimum is, therefore, deemed to represent a state of optimum autoregulation, and CPP-based management that targets this level has been associated with better outcomes.<sup>92,93</sup>

An autoregulation-guided approach to individualise CPP might be helpful in preventing cerebral hypoperfusion while avoiding the risks of excessive cerebral blood flow. An approach based on optimisation of autoregulation is physiologically attractive and has the potential to reconcile perfusion-supporting and oedema-minimising treatments. However, autoregulation can be impaired in a region-specific way that might not be captured by the PRx, which is a global average. Alternative measures based on assessment of blood flow or brain tissue oxygen reactivity have the opposite limitation of restricted global spatial coverage. Prospective evidence from clinical studies is urgently needed before definitive guidelines can be drawn up.

#### Multimodal monitoring for individualised management

Simultaneous use of several monitoring modalities could provide a means of targeting patient-specific ICP thresholds.<sup>66</sup> Concordant changes identified from different measures provide cross-validation of the physiological state of the injured brain. For example, a critical PbtO<sub>2</sub> reduction could be used to individualise thresholds for more aggressive methods for correcting low CPP due to high ICP. Conversely, discordant findings, although potentially posing a clinical dilemma in terms of treatment compromise, might sometimes offer clues to the presence of pathophysiological heterogeneity and stimulate the





**Figure 3:** Screenshot showing computerised multimodal monitoring for traumatic brain injury

Advanced invasive monitoring for patients with traumatic brain injury (TBI) can simultaneously provide time trends for mean intracranial pressure (ICP), arterial blood pressure (ABP) readings, the pressure-reactivity index (PRx), a derived autoregulation index (presented both as a time trend and as a colour-coded warning bar), measures of brain tissue partial tension of oxygen (PbtO<sub>2</sub>), and three microdialysis variables (glycerol [GLY], lactate:pyruvate ratio [LPR], and glucose [GLC]), all shown in the first column. It is helpful to integrate the signals into one bedside screen with trend charts showing current and historical values to allow early detection and accurate assessment of newly developing second insults. Other crucial information can be obtained from the neuromonitoring signals and presented on the same screen (second column) to further facilitate decision making. This includes information about the current (and historical) state of cerebral autoregulation and the related cerebral perfusion pressure (CPP) safe zone recommendation. These are depicted in the second column as CPP; end tidal CO<sub>2</sub> (an estimate of partial pressure of CO<sub>2</sub> in the blood [ETCO<sub>2</sub>]); two optimum CPP representations (the estimated CPP range corresponding to intact autoregulation [in green] and an error bar chart summarising the PRx / CPP relation [the optimum CPP value is at the vertex of the fitted curve]); and the time percentage of a given CPP value (represented by the histogram at the bottom of the second column). Total (or recent) doses of intracranial hypertension or brain hypoxia (as indicated by PRx, ICP, and PbtO<sub>2</sub>, with insult regions highlighted in red), and the state of homeostatic decomplexification (as indicated by the ICP complexity chart [CI(ICP)], a multiscale entropy representation) are shown in the third column.

search for less well recognised routes to energy failure, such as diffusion hypoxia,<sup>71,72</sup> mitochondrial dysfunction,<sup>94</sup> and low cerebral glucose levels<sup>83,95</sup> as downstream markers of compromised cerebral perfusion.

However, current multimodal monitoring generates vast amounts of data, which might need to be summarised for clinicians to extract information that can be used to guide patients' care (figure 3). Advances in monitoring will probably also depend on advances in neuroinformatics and data analysis.<sup>96</sup> Computer visualisation techniques offer a promising way to reduce complex datasets to a form that can be interpreted by clinicians and have been applied in various areas, including investigation of the cumulative burden of intracranial hypertension<sup>97</sup> and assessment of autoregulation.<sup>98</sup> Such complex multi-dimensional problems are not new outside medicine, and other so-called big data techniques will very likely find increasing application in the intensive care of patients with TBI.<sup>99</sup>

### Physiological monitoring in elderly people

Use of advanced multimodal monitoring to guide management in older patients is conceptually appealing,

but experience in this area is scarce. This lack of experience is in part accounted for by the increased risks of invasive intracranial monitoring in older patients, who frequently present on anticoagulant and antiplatelet drugs (panel), and in part by the expectation of poor outcome that has made aggressive monitoring and therapy less frequent in this age group. Changing attitudes might provide more data to guide individualisation of treatment for older patients in the future, and development of less invasive monitoring methods would be particularly beneficial in this group.

### Targeted ICU management with aggressive therapies

No treatments in the ICU are risk free, and the more aggressive interventions for restoring cerebral homeostasis have substantial potential to cause harm (figure 2). Multimodal monitoring can show that aggressive interventions are justified by proving that cerebrovascular physiology is seriously compromised (eg, ICP and CPP outside the thresholds, PbtO<sub>2</sub> reductions, or elevations in lactate and lactate:pyruvate ratio), and not amenable to therapy with less risky interventions. Once a therapeutic

target has been identified, careful measurement of physiological variables can minimise harm for some interventions.

### Augmentation of CPP

Pharmacological augmentation of CPP might improve cerebral oxygenation but at the expense of serious cardiopulmonary complications.<sup>100</sup> Advanced cardiovascular monitoring—including intravascular volume assessment, echocardiography, or cardiac output—beyond standard pulse oximetry and invasive arterial pressure monitoring might be necessary.<sup>66</sup>

### Hypocapnia

A brief period of hypocapnia could be justifiable in the face of an episode of dangerously high ICP but it might cause ischaemia through vasoconstriction,<sup>101</sup> particularly in the early phases after injury. For this reason, measurement of cerebral oxygenation—most commonly by PbtO<sub>2</sub> monitoring—is recommended when hypocapnia is used, to minimise the ischaemic risk.<sup>66</sup>

### Metabolic suppression

Barbiturates for metabolic suppression are effective in reducing ICP but carry substantial risks of cardiovascular instability and other end-organ dysfunction or metabolic disturbances.<sup>102</sup> Advanced cardiovascular monitoring and support—including fluid titration, inotropes, and use of vasopressors—is advisable to avoid arterial hypotension.

### Hypothermia

Hypothermia, a treatment with strong neuroprotective action in animal models,<sup>103</sup> failed to show outcome benefit in clinical trials.<sup>61</sup> When moderate hypothermia (32–35°C) was used as an early ICP intervention, the treated group had a worse outcome than did controls.<sup>61</sup> Despite the results of this trial, hypothermia continues to be used in some centres but typically with higher ICP thresholds (25–30 mm Hg),<sup>104</sup> denoting an implicit acceptance that the risks of hypothermia demand more deranged physiology before the risk:benefit ratio becomes favourable.

### Decompressive craniectomy

Decompressive craniectomy is effective at reducing ICP, but results of RCTs have shown differences in outcome depending on the target group. In the DECRA trial,<sup>60</sup> decompressive craniectomy did not improve outcome when used for modest ICP increases. However, the balance of risk and benefit changes in circumstances for which aggressive therapies are justified by the presence of refractory severe intracranial hypertension. For example, in the RESCUE-ICP study,<sup>105</sup> decompressive craniectomy targeted to patients with refractory severe ICP was shown to reduce mortality and shift neurological outcomes so that more patients could at least function independently at home, although these gains were

achieved at the expense of increases in survival with severe disability.

These findings emphasise the importance of following a graded sequence for aggressive interventions, beginning with those with least potential for harm before escalating to higher—and potentially more harmful—therapeutic intensity (figure 2). Furthermore, the evidence highlights the need to select interventions on the basis of the clinical picture in individual patients and the circumstances at the time of intervention. Further research into the contribution of the physiological monitoring methods might enable more refined stratification of patients for these more aggressive therapies.

### Aggressive therapies in elderly patients

Aggressive therapies are linked to severe side-effects and might not be tolerated by frail older patients with impaired physiological reserve (panel). The high incidence of cardiorespiratory comorbidities in such individuals might further reduce the ability of patients to tolerate some of the aggressive interventions (eg, augmentation of CPP, barbiturates, and hypothermia) used in the critical care of TBI. Therefore, careful monitoring of systemic physiology is mandatory, and caution is needed with haemodynamic augmentation and second-tier therapies for high ICP in these patients.

In two major RCTs on decompressive craniectomy for TBI,<sup>60,105</sup> patients older than 65 years were excluded, probably reflecting the scepticism of the neurotrauma community about use of aggressive therapies in older people. In another study, decompressive craniectomy was used to treat unilateral or bilateral brain swelling in 44 patients with TBI older than 66 years;<sup>106</sup> however, mortality was 77% and overall unfavourable outcomes were recorded in 82%, leading to this approach being abandoned in clinical practice for elderly patients who present with a GCS of 8 or less.

### Emerging opportunities in the management of severe TBI

The focus of this Review has been on how we might improve clinical management of TBI using techniques that are already available, even if not used widely in clinical practice. However, emerging advances could deliver additional refinement, or even paradigm changes, in how we treat these patients, with respect to better characterisation of TBI, identification of novel therapeutic targets, and generation of evidence to support changes in management. Pharmacological trials of erythropoietin<sup>107,108</sup> and progesterone<sup>109,110</sup> for TBI failed to show improvement in neurological outcome despite experimental evidence of multiple neuroprotective mechanisms, thus underlining the importance of targeting treatments to selected groups of patients. Enrolment criteria in these trials were based on severity of TBI, and the benefits of compounds acting on specific pathways might not have been demonstrable in a heterogeneous population of patients with TBI.

Future trials should aim to select patients on the basis of specific mechanisms of brain damage in individual patients to maximise potential for improved outcomes.

The growing use of MRI in TBI promises to provide better definitions of injury location, type, and severity;<sup>111</sup> moreover, accumulating data linking genetic variability to outcome<sup>112</sup> suggest that we might be able to identify patients in whom specific therapies could be effective. For instance, once the pathological role of spreading depression is clarified better and patient groups who are likely to be affected have been identified, specific interventions—eg, nimodipine or ketamine—could be envisaged to correct spreading depression.<sup>113</sup> Promising therapeutic targets are emerging from more rigorous preclinical evaluation of new interventions for TBI, such as those delivered by Operation Brain Trauma Therapy, a multicentre multiplatform collaboration for experimental evaluation of therapies.<sup>114</sup> Other basic biology research that might advance clinical interventions for mitigation of secondary injury includes identification of the sulfonylurea receptor (SUR1), which is implicated in oedema formation and contusion expansion,<sup>115</sup> preclinical assessment of novel brain fuels that bypass impaired energy metabolism,<sup>116</sup> and more precise targeting of the inflammatory response,<sup>117</sup> which is emerging as a key player in TBI pathophysiology.

## Conclusions and future directions

Advances in monitoring provide a paradigm that could enable us to move treatment of TBI in the ICU from a standard one-size-fits-all approach to more individualised treatment. Better identification of disease mechanisms as potential targets for intervention seems a reasonable aspiration. Improved characterisation of mechanisms might also offer new goals for neuroprotective drug development. However, translational failure of a few biologically and experimentally well founded interventions<sup>118</sup> suggests that uncharacterised patient factors are still a major stumbling block in terms of tailoring aggressive treatments to maximise benefit and minimise harm at an individual level. Despite the wealth of data, stratification of patients into subgroups with more homogeneous pathophysiology, disease course, and expected outcome is still at an early stage.

Integration of newer monitoring modalities could provide further individualisation of therapy, but these approaches rely on data that do not come from RCTs based on targeted approaches. Indeed, the results and subsequent discussion of the BEST:TRIP trial of ICP monitoring<sup>57,58</sup> highlight the difficulties with using classic RCTs to evaluate monitoring devices and treatment thresholds, and we might need to rely on other means of evidence generation—eg, comparative effectiveness research—to provide strong frameworks for use of newer monitoring devices in TBI. Such approaches will need large, well characterised populations of patients with rigorous outcome assessment. International initiatives—

## Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 2010, and March 6, 2017, with the terms “head injury”, “traumatic brain injury”, “intensive care”, “epidemiology”, “intracranial pressure”, and “head injury OR traumatic brain injury AND elderly”. Only papers published in English were included, and except for a review on neuroprotection based on experimental data, animal studies were excluded. Additional papers or websites were identified by searching the authors’ personal files.

eg, the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) and other partner studies in the International Traumatic Brain Injury Research initiative (InTBIR)—could generate the large samples needed to address this aim and provide the context for developing and testing precision medicine approaches in severe TBI.

The epidemiological shift towards a larger proportion of physiologically fragile elderly patients with TBI in high-income countries calls for varying preventive approaches, such as measures aimed at frailty and falls,<sup>119</sup> and suggests the need for changes in ICU management approaches. Less-invasive monitoring methods, for instance, might improve care and reduce side-effects during the acute phase. Techniques for quick and efficient restoration of coagulation could limit brain injury progression in patients on anticoagulant and antiplatelet drugs, thus improving outcomes. Provision of care based on measured, rather than assumed, outcome could avoid self-fulfilling prophecies of inevitable poor outcome for older patients. Age older than 65 years has often been an exclusion criterion in clinical trials of interventions for TBI—eg, decompressive craniectomy and neuroprotective drugs<sup>52,60,105,108,120</sup>—leading to the paradox that a population segment at increased risk of TBI has not been exposed to possible therapeutic interventions. In view of the logistic complexities of undertaking RCTs in TBI generally, and specifically in older patients, comparative effectiveness research approaches might also facilitate assessment of interventions in older patients, with differences in management of these individuals in various centres providing an appropriate context to undertake such studies.

The changes described here hold promise for reshaping current management in the ICU and potentially improving outcome. However, showing that this promise can be fulfilled requires rigorous research evaluation and proof of cost-effectiveness.

## Contributors

NS designed the review structure and did a preliminary bibliographic search. All authors discussed the general outline of the review and agreed on a writing plan. NS, MC, and TZ coordinated the writing and the literature search, assembled a preliminary draft, and incorporated further contributions from each author into subsequent versions. GC and MBS reviewed current ICU treatment. AE, PS, and DKM focused on targeting

For more on **CENTER-TBI** see <https://www.center-tbi.eu>

For more on **InTBIR** see <https://intbir.nih.gov>

For more on **Operation Brain Trauma Therapy** see <http://www.safar.pitt.edu/obtt>

mechanisms and multimodal monitoring. TZ and MC collected and discussed evidence concerning the ageing population. DKM extensively edited the paper. All authors reviewed and commented on several preliminary drafts and approved the final version of the review.

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MBS reports speakers' fees from COVIDIEN, Astellas Pharma, Axis Shield, and Orion and a grant from GE Healthcare, outside the submitted work. PS receives part of the licensing fees for multimodal brain monitoring software ICM+, licensed by Cambridge Enterprise Ltd, University of Cambridge, UK. DKM reports personal fees for consultancy work or as a member of data monitoring committees for Solvay, GlaxoSmithKline, Brainscope, Ornim Medical, Shire Medical, and Neurovive, and honorarium for a lecture at the London Hospital, UK, reimbursed to organisers by GlaxoSmithKline. NS, MC, GC, AE, and TZ declare no competing interests.

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